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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,217	06/13/2001	Kathleen Danenberg	11220/129	6207

23838 7590 02/14/2003

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	15

DATE MAILED: 02/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,217	DANENBERG, KATHLEEN6	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-16 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. Applicant now complies with the requirements for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

Double Patenting

2. Claims 12-16 and 23-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-11, 17-22 and 26 of copending Application No. 09/842,111 in view of Gonzalez et al (U.S. Patent 6,015,673).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to determining the effectiveness and safety of a 5-fluorouracil based chemotherapeutic regimen by analyzing the mRNA expression of the DPD gene using the same primer sets. These claims differ only in the step of determining the 5-fluorouracil based regiment based upon the DPD mRNA concentration.

Gonzalez teaches a method for determining the level of DPD gene expression in a tissue to determine the safety of a 5-fluorouracil based chemotherapeutic regimen comprising the steps: (see column 14, lines 41-51, also see column 27, lines 14-27, here the tissue is cultured fibroblasts derived from skin biopsies),

(a) obtaining a sample from a patient (column 14, lines 41-52)

(b) isolating mRNA from the sample (column 14, lines 52-67),

(c) amplifying the mRNA with primers which are substantially identical to SEQ ID NO: 1 and 2 (see column 55, SEQ ID NO: 5)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the DPD analysis method of copending Application 09/842,111 to determining the safety of 5-fluorouracil based chemotherapeutic regimens since Gonzalez states "The method and compositions are useful for identifying persons who are at risk of a toxic reaction to the commonly employed cancer chemotherapy agent 5-fluorouracil (see column 1, lines 8-10)". It is noted that these claims were not subject to restriction from one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112 – Scope of Enablement

The rejection of claims 6-26 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in view of the amendments and arguments.

Claim Rejections - 35 USC § 112 – Written Description

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-16 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

All of these claims encompass nucleic acids which are different from those disclosed in the specific SEQ ID Nos, which include variants for which no written description is provided in the specification. Specifically, the claims encompass "80% identical" oligonucleotides, but the specification give only certain specific oligonucleotides as examples of such primers and probes.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen).

> It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, a certain subset of specific SEQ ID NOs is described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or description of any nucleic acids which are substantially identical to SEQ ID Nos: 1, 2, 7 and 8. This larger genus encompasses, according to the definition of the specification, anything which is at least 80% homologous with possible insertions and deletions. For example, a 20 mer of fixed sequence has 60 different possible point mutations. The first position can be changed from the current nucleotide to one of the other three, as can the second, and the third

through 20th. Of course, 3 times 20 equals 60. For two changes or 90% homology, there are the 60 positions which can be changed times the 57 possible changes for the second position (since the first position is already addressed, this is 19 x 3). 60 + (60 x 57) = 3480. For four changes, or 80% homology, the result would be (60 + (60 x 57) + (60 x 57 x 54) + (60 x 57 x 54 x 51) which equals 9, 606, 840 different possible configurations. This is an extremely substantial variation. The stringency of hybridization language is not limiting, since no particular stringency is required, so this does not impose any structural limitation on oligonucleotides. Even if such conditions were imposed, this would not substantially reduce the size of the undescribed genus of over 9 million different possible oligonucleotides, for which Applicant has identified only 1. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 12-13, 15-16 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (U.S. Patent 6,015,673) in view of Willhauck et al (Biotechniques (1998) 25:656-659).

Gonzalez teaches a method for determining the level of DPD gene expression in a tissue to determine the safety of a 5-fluorouracil based chemotherapeutic regimen

comprising the steps: (see column 14, lines 41-51, also see column 27, lines 14-27, here the tissue is cultured fibroblasts derived from skin biopsies),

(a) obtaining a sample from a patient (column 14, lines 41-52)

(b) isolating mRNA from the sample (column 14, lines 52-67),

(c) amplifying the mRNA with primers which are substantially identical to SEQ ID NO: 1 and 2 (see column 55, SEQ ID NO: 5)

a sequence, SEQ ID NO: 5, which is a sequence substantially identical to the claimed SEQ ID NO: 1 as shown in the alignment below.

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Gonzalez SEQ ID NO: 5 -  GCAAGGAGGGTTTGTCACTG
                         ||||||||||||||||
Claimed SEQ ID NO: 1 AGGAGCAAGGAGGGTTTG
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As the alignment shows, the Gonzalez primer sequence is 14/18 nucleotides identical to the claimed sequence, for a homology over the claimed sequence of 73%.

Further, Gonzalez teaches the complete sequence, 100% identical, of the claimed SEQ ID NO: 1 at nucleotides 37-56 of SEQ ID NO: 1 (see columns 29 and 30) as well as the complete sequence of the claimed SEQ ID NO: 2 at nucleotides 101-120 of SEQ ID NO: 1 (see columns 29 and 30) as well as the complete sequence of the claimed SEQ ID NO: 7 at nucleotides 637-659 of SEQ ID NO: 1 (see columns 29 and 30) as well as the complete sequence of the claimed SEQ ID NO: 8 at nucleotides 702-722 of SEQ ID NO: 1 (see columns 29 and 30).

Further, all of the SEQ ID NO:s are identical to the human DPD sequence disclosed in SEQ ID NO: 1 of U.S. Patent 5,856,454 and are derived from that sequence.

Gonzalez teaches freezing of the sample (see column 25, line 64) as well as fixing of the sample for detection (see column 13, lines 46-53).

Gonzalez teaches isolation of mRNA in the presence of Guanidine, a chaotropic agent (column 14, lines 52-67).

Gonzalez teaches that appropriate samples include any cells from the patient that may express the DPD gene (column 14, lines 41-51).

Gonzalez teaches a threshold for the mutation in which there is a problem tolerating 5-fluorouracil based chemotherapeutic regimens where a 2 fold difference will yield enhanced risk (see column 15, lines 1-11)

Gonzalez does not teach step (d) comparing the amount of DPD mRNA to the amount of mRNA of an internal control gene.

Willhauck teaches comparing the amount of the target gene to an internal control gene (see page 656, columns 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the internal controls of Wilhauck in the method of Gonzalez since Wilhauck states "Taken together our results show that the internal control circumvents a number of inherent problems of alternative controls to assess pre-PCR procedures. The overall RT-PCR assay sensitivity can be reliably evaluated on a per sample basis and the sensitivity limit of the RT-PCR assay can be assessed for every sample. This type of reliability can improve the homogeneity of results from clinical investigations in the future (page 658, column 3 to page 659, column 1)". An ordinary practitioner would have been motivated to use the internal controls of Wilhauck

in the method of Gonzalez in order to reliably and sensitively improve the homogeneity of the clinical results.

Response to Arguments

8. Applicant's arguments filed January 24, 2003 have been fully considered but they are not persuasive.

Applicant first argues, with regard to the written description rejection, that the current claims have structure and function. This argument is not correct because the structural limitation is clearly insufficient. In Lilly, there was also structure, the prior art rat insulin protein, which shared 80% homology with the human insulin sequence. However, in Lilly, this 80% homology was found insufficient to support the claim to the human insulin sequence. Consequently, in the current case, where the 80% homology is tied solely to functional elements which are inherent in sequences, the claims remain insufficiently described. In the written description guidelines, the examples of functional language relate to required structural motifs which guide the practitioner in altering the molecules. The current functional language does not provide guidance on changes, since there are no motifs which need be conserved. Here the function, amplification, is available to any sequence whatever. That is, any sequence mixed with exon 1 of DPD would be "capable" of amplifying that sequence to some extent. For example, random hexamers are frequently used for such amplifications. Therefore, the function identified by Applicant is not sufficient to distinguish the primer requirements in any meaningful way.

Applicant then argues that there would be no motivation to select the specific, slightly adjusted primers claimed. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the Gonzalez prior art as useful for primers and probes for the detection of DPD, and in particular for diagnosis of whether to use 5-fluorouracil, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Applicant then argues that amplification from fixed tissue represents a greater technical challenge. This argument is not persuasive for several reasons. First, there is no evidence on the record that the primers of Gonzalez would not function to amplify fixed and embedded tissue and the ordinary practitioner would expect such primers to function on any tissue from which amplifiable nucleic acid is available. If such evidence of an unexpected result were shown, the claim would necessarily need to be narrowed

to the scope of that unexpected result, which would be the oligonucleotide sequence of the particular primer shown to have this function. Second, the claim simply requires that the primer be capable of such an amplification, and the primer of Gonzalez is clearly "capable of" amplifying any cDNA or mRNA isolated from tissue if the sequence matches.

Applicant then argues this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art of Gonzalez that the primers would function in amplification reactions (see figures 5 and 7, for example). This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art

> gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of the specific primer with a specific sequence for the specific purpose of amplifying DPD. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of the primer for amplification of DPD.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

February 13, 2003